



**Rejection Under 35 U.S.C. § 103(a)**

Claims 23-58 are rejected as unpatentable over Sugiura, K. and H.M. Wuest "Effect of Thalidomide on Transplantable Mouse, Rat, and Hamster Tumors" *GANN*, 55, 57-60, February 1984 ("Sugiura"); or over United States Patent No. 5,399,363 to Liversidge et. al. ("Liversidge"). The Examiner contends that Sugiura states repeated interperitoneal injections of thalidomate (1000 mg/kg/day) had a moderately inhibitory effect on lewis bladder carcinoma. The Examiner also contends that Liversidge teaches thalidomide as an anticancer agent. Applicants respectfully traverse the Examiner's rejection.

In order to properly determine a prima facie case of obviousness, an Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." Manual of Patent Examining Procedure §2142 (8th ed., August 2001). This is important, as "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." *Id.* Three basic criteria must then be met: first, there must be some suggestion or motivation to modify or combine the cited references; second, there must be a reasonable expectation of success; and third, the prior art references must teach or suggest all the claim limitations. *Id.* at § 2143. With regard to the first criterion, it is important to recognize that the "mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *Id.* at 2143.01 (emphasis in the original) (citing *In re Mills*, 916 F.3d 680 (Fed. Cir. 1990)).

In regard to Sugiura, the Examiner has relied solely on the abstract of the reference. The complete text of Sugiura has been provided herewith to complete the record.<sup>1</sup>

As stated above, Applicant claims a method of inhibiting tumor formation and a method of inhibiting tumor metastasis using an angiogenesis-inhibiting amount thalidomide. Sugiura in no way discloses or suggests the method of inhibiting tumor formation as claimed by the Applicant. On page 59, Sugiura states "Thalidomide had no inhibitory effect on the growth of 18 kinds of mouse, rat, and hamster tumor." Sugiura

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<sup>1</sup> Applicant respectfully requests that the Examiner execute the enclosed PTO Form-1449 to indicate consideration of the entire reference. [Sugiura, K. and H.M. Wuest "Effect of Thalidomide on Transplantable Mouse, Rat, and Hamster Tumors" *GANN*, 55, 57-60]. No fee is believed to be due. However, if the Examiner determines that any fee is due, please charge the required fee to Pennie & Edmonds LLP Account No. 16-1150.



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Further teaches that thalidomide only had slight inhibiting effect on six of the tumors treated

and only had moderate inhibition of one tumor at 1000mg/kg/day. Indeed, Sugaira teaches away from the Applicant's claimed method. Specifically, the teaching of no activity against 18 tumors and only slight inhibition at 1000mg/kg/day teaches away from the angiogenesis-inhibiting methods claimed by the Applicant. Significantly, Sugaira references a DiPaolo article which reported "thalidomide (500mg/kg/day) was ineffective against 8 transplantable animal cancers." In stark contrast, Applicant has surprisingly discovered the anti-angiogenic properties of thalidomide and claimed the inhibition of tumor formation using amounts of about 300 mg/kg/day or less. Applicant therefore respectfully submits that claims 23-57 are not obvious over Sugaira. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of claims 23-57 under 35 U.S.C. §103(a).

In regard to Liversidge, the Examiner has relied on Column 3, lines 46-49 of the Liversidge patent in alleging that the claims are obvious. The Examiner contends that Liversidge's contention that "the anticancer agent can be an immunosuppressive drug, such as, for example, cyclosporine, azathioprine, sulfasalazine, methoxsalen, and thalidomide" renders Applicant's method of inhibiting tumor formation using an angiogenesis-inhibiting amount thalidomide obvious. Applicant respectfully traverses as this statement does not suggest all the claim limitations nor satisfy the legal requirement for a prima facie case of obviousness.

At the time of Liversidge, thalidomide was not known to be an anticancer agent. Liversidge's misleading statement does not change that fact. At the relevant time, each of the compounds referred to by Liversidge were merely immunosuppressive agents. According to The Merck Index, *Twelfth Edition*, cyclosporine is therapeutically categorized as an immunosuppressive agent; azathioprine is an immunosuppressive agent and an antirheumatic agent; methoxsalen is a pigment, and sulfasalazine is an ulcerative colitis agent and effective against Crohn's disease. Similarly, thalidomide was at the time and after Liversidge's disclosure therapeutically classified only as an immunomodulatory compound and a sedative [The Merck Index, 12<sup>th</sup> ed., Whitehouse Station: Merck, 1996]. Neither of these therapeutic uses teach or would suggest that thalidomide would have anticancer activity. Significantly, nowhere in Liversidge are the immunosuppressive compounds specifically shown to be effective as anticancer agents. The mere statement that an "anticancer agent can be an immunosuppressive drug" does not provide an adequate suggestion of Applicants' method of inhibiting tumor formation using an angiogenesis-inhibiting amount thalidomide,



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much less provide the requisite suggestion of the dosages or for the specific tumors claimed by the Applicant.

Finally, the mere allegation in Liversidge does not provide a reasonable expectation of success. *In re Fine* 837 F.2d 1071, 1075. Even if one were to choose an immunosuppressive drug from the list for incorporation into Liversidge's particles, there is no teaching to suggest that they will be effective to have angiogenesis inhibiting effects for inhibition of tumor growth. In sum, Liversidge, at best, suggests that immunosuppressive agents can be tried in Liversidge's delivery method -- not for cancer. Even assuming, *arguendo*, that Liversidge's statement was accurate it merely provides an invitation to experiment. As the Examiner knows, "obvious to try" is not the proper legal standard. *In re O'Farrel* 853 F.2d 894, 903. In sum, this unsupported allegation fails to provide the requisite legal suggestion plus reasonable expectation of success, but also is premised on unsound scientific basis. Immunosuppressive agents are not antitumor agents. Applicant therefore respectfully submits that claims 23-57 are not obvious over Liversidge. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of claims 23-57 under 35 U.S.C. §103(a).

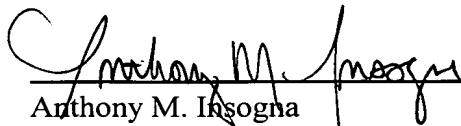
### **Conclusion**

Applicants respectfully request that the above remarks and accompanying documents be entered in the present application file. Applicants also respectfully request withdrawal of the outstanding rejections. An early allowance of the present application is respectfully requested.

No fee is believed due. However, if the Examiner determines that any fee is due, please charge the required fee to Pennie & Edmonds LLP Account No. 16-1150.

Respectfully submitted,

Date: September 19, 2002

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Enclosures